Annals of Clinical and Analytical Medicine
Original Research

Diagnostic value of mid-regional pro-atrial natriuretic peptide (MR-proANP) level in patients with acute pulmonary embolism

Ertuğrul Altuğ[1], Hasan Kara[2], Ayşegül Bayır[2], Ahmet Ak[2], Seyit Ali Kayış[3], Ali Ünlü[4], Bülent Behlül Altunkeser[5], Mustafa Koplay[6], Abdullah Tunçez[5], Hüseyin Tezcan[7]
[1] Department of Emergency Medicine, Başaksehir Çam and Sakura State Hospital, Istanbul
[2] Department of Emergency Medicine, Faculty of Medicine, Selcuk University, Konya
[3] Department of Biostatistics and Medical Informatics, Faculty of Medicine, Bolu İzzet Baysal University, Bolu
[4] Department of Medical Biochemistry, Faculty of Medicine, Selcuk University, Konya
[5] Department of Cardiology, Faculty of Medicine, Selcuk University, Konya
[6] Department of Radiology, Faculty of Medicine, Selcuk University, Konya
[7] Department of Cardiology, Ministry of Health Konya City Hospital, Konya, Turkey

Abstract

Aim: Right ventricular failure can develop in patients with pulmonary embolism (PE) and is associated with increased mortality. Mid-regional pro-atrial natriuretic peptide (MR-proANP), a natriuretic peptide, is secreted due to the increased atrial wall tension caused by right heart failure. In this study, we aimed to investigate the diagnostic value of MR-proANP in patients who presented to the emergency department with a pre-diagnosis of pulmonary embolism.

Material and Methods: Among patients with a preliminary diagnosis of PE, 100 patients who were confirmed to have PE by computed tomography pulmonary angiography (CTPA) were determined as the case group. As a control group, 50 patients were randomly identified, in whom the diagnosis of PE was excluded. Echocardiography was performed in all patients in the case group immediately after the diagnosis was confirmed, and the presence of right ventricular dysfunction was investigated. This study was designed as a prospective observational study.

Results: The median value of MR-proANP (645.8 (66.37-3313.08) pmol/L) in the case group was found to be significantly higher than median value of MR-proANP (442.9 (226.73-774.78) pmol/L) in the control group (p:0.003). MR-proANP was found to be significantly higher in the differential diagnosis of PE.

Discussion: In addition to clinical signs and symptoms, MR-proANP levels seem to be a useful variable that may improve diagnostic accuracy in patients with suspected pulmonary embolism in the emergency department.

Keywords

MR-proANP, Acute Pulmonary Embolism, Right Ventricular Failure, Biomarker

DOI: 10.4328/ACAM.21399 Received: 2022-09-19 Accepted: 2022-10-28 Published Online: 2022-10-29 Printed: 2023-01-01 Ann Clin Anal Med 2023;14(1):21-24
Corresponding Author: Ertuğrul Altuğ, Department of Emergency Medicine, Başaksehir Çam and Sakura State Hospital, Istanbul, Turkey.
E-mail: ertugrulaltug42@gmail.com P: +90 535 656 84 42
Corresponding Author ORCID ID: https://orcid.org/0000-0001-6807-643X
This study was approved by the Ethics Committee of Selcuk University (Date: 2018-03-16, No: 2018/153)

Introduction

Pulmonary embolism (PE) refers to the clinical picture that develops as a result of complete or partial occlusion of the pulmonary artery by ruptured thrombus fragments and generally originates from the venous system [1] . PE is mostly caused by blood clots in the lower extremity deep vein system [2]. PE ranks third among the diseases that cause mortality in the context of cardiovascular system diseases, after acute coronary syndrome and cerebrovascular event [3].

PE has a wide spectrum of clinical presentations, and is difficult to diagnose due to the lack of a specific clinical presentation [4]. Therefore, the most important step for the diagnosis of PE is clinical suspicion. To confirm the diagnosis of PE, it is important to evaluate the risk factors, symptoms, physical examination findings, radiological and laboratory tests as a whole [5].

In patients with PE, right heart functions deteriorate as a result of increased pressure in the pulmonary embolism artery that develops proximal to the thrombus. Echocardiography (echo) is used to assess the size and function of the right heart and diagnose right heart failure [6].

In 1981, as a result of a long-term study, de Bold et al. first identified atrial natriuretic peptide (ANP), which is secreted from atrial myocardial cells and exerts diuretic and natriuretic effects in rats [7]. ANP is produced as a result of increased atrial Wall tension. Since the half-life of the 126 amino acid part of ANP, known as ProANP, is longer, its serum value can be determined as mid-regional pro-ANP (MR-proANP) with newly developed methods [8]. It has been determined that in patients diagnosed with PE, the MR-proANP values are increased and may provide value in the diagnosis of PE [9,10].

The main purpose of our study was to determine whether or not the increase in the MR-proANP levels is a useful biomarker in the diagnosis of PE.

Material and Methods

Study Design: The present study was designed as a prospective and observational clinical study with case and control groups. The study included patients admitted to the 3-level university hospital emergency medicine department with the suspicion of PE between May 2018 and May 2019. Patients who were diagnosed with PE, had no exclusion criteria and agreed to participate in the study were included in the case group. Patients under the age of 18, pregnant women, trauma patients and patients who did not accept to participate in the study were excluded from the study. The definitive diagnosis of PE was made using 256-slice computed tomography pulmonary angiography (CTPA). The case group consisted of 100 patients with a definite diagnosis of PE by BTPA, and the control group consisted of 50 randomly selected patients without a preliminary diagnosis of PE. Blood samples of the patients included in the study were analyzed in the biochemistry laboratory of the same hospital using the ELISA method. Patient results were calculated as pmol/L according to the calibration table. In this study, all patients admitted to the emergency department with acute PE underwent echo examination. Echo examination of all patients was performed by the same operator.

Statistical Analysis: Descriptive statistics such as mean, standard deviation, minimum and maximum were applied for features that showed continuous variation. Absolute and percentage frequencies were applied for categorical variables. Before the statistical analysis, the Anderson-Darling test was used to determine whether the data showed a normal distribution or not. The MR-proANP level (and other continuous variables) was found to show a non-normal distribution, and the transformation was not enough to stabilize the variance. Consequently, the Kruskal-Wallis test was used for the multi-group comparisons, and the Mann-Whitney U test was used to determine the different group or groups. Two-way tables were obtained from the categorical data and whether the levels of these two variables were independent or not was tested with the Chi-square test. A p-value of <0.05 was considered significant in the statistical test. All statistical analyses were carried out with the R software.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

The demographic and clinical characteristics of the case and the control groups included in the study are summarized in Table 1.

The median MR-proANP value in the case group was found to be significantly higher than in the control group (p:0.003). While the median (min.-max.) Mr-proANP value was 645.8 (66.37-3313.08) pmol/L in the case group, this value was found to be 442.9 (226.73-774.78) pmol/L in the control group.

Since the Wells' scoring system was applied to only the case group, no comparison could be made with the control group. In the Wells' scoring system, there were 55 (55%) patients in the low-risk group, 36 (36%) in the medium-risk group and 9 (9%) in the high- risk group. The common MR-proANP median (min.-max.) value of the low- and medium- risk group was 226.7 (157.1-603.7) pmol/L, and the MR-proANP median (min.-max.) value of the patients in the high-risk group was 877 (272-2122)

Table 1. Demographic and Clinical Characteristics of the Case and the Control Group Patients

Age*	68.5 (18-91)	67 (22-90)	0.271#
Gender** (Female/Male)	60/40	28/22	0.639##
Vital parameters			
Systolic Blood Pressure*	120 (80-210)	130 (90-200)	0.025#
Diastolic Blood Pressure*	70 (30-140)	80 (40-110)	0.054#
Heart rate*	109 (51-220)	81.5 (47-138)	0.052#
Fever*	36.6 (34-39.8)	36.55 (36-38)	0.595#
Saturation*	88 (50-98)	96 (90-99)	0.001#
Respiratory Rate*	21.5 (12-46)	18 (13-23)	0.001#
Comorbidity (Yes/No)			
Diabetes Mellitus**	35/65	17/33	0.903##
Hypertension**	53/47	25/25	0.729##
Coronary Artery Disease**	30/70	20/30	0.221##
Malignancy**	24/76	0/50	<0.05##
COPD**	29/71	6/44	<0.05##
Trauma within 4 weeks**	14/86	0/50	<0.05###
Congestive Heart Failure**	17/83	0/50	<0.05##
Pulmonary Embolism**	2/98	0/50	0.553###
Deep Vein Thrombosis**	11/89	0/50	<0.05###

* Median (min-max); ** Number of Individuals; # Determined by the Mann-Whitney U test; ## Determined by the Pearson Chi-Square test; ### Determined by the Fisher's Exact test

Table 2. Wells' Scoring System Distribution Features of The Case Group

	Low-Moderate	High	p value
MR-proANP (pmol/L)*	226.7 (157.1-603.7)	877 (272-2122)	0.03#

* Median (min-max); #Determined by the Mann-Whitney U test

Table 3. Echo Findings, Case Distribution and Median MR-proANP Values of the Case Group

	MR-proANP (pmol/L)*		p value
	Normal	Pathological	
PAP	303.35 (114.84-3313.08)	233.25 (66.37-2830.26)	0.461#
RAA	246.62 (87.65-3313.08)	255.62 (66.37-2700.11)	0.502#
TAPSE	529.18 (66.37-2700.11)	210.92 (87.65-3313.08)	0.01#

* Median (min-Max) # Determined by the Mann-Whitney U test

pmol/L (p:0.03) (Table 2).

The median MR-proANP value in the case group was found to be significantly higher compared to the control group (p:0.003). The median (min.-max.) MR-proANP value was 645.8 (66.37-3313.08) pmol/L in the case group, whereas this value was found to be 442.9 (226.73-774.78) pmol/L in the control group. After being diagnosed with PE, all patients in the case group underwent echo that was performed by a single cardiologist. The Right Atrium Area (RAA), Pulmonary Artery Pressure (PAP) value and Tricuspid Annular Plane Systolic Excursion (TAPSE) values were measured with echo to detect right heart failure in all patients. Among the patients diagnosed with PE, the numbers of patients with normal PAP value, RAA and TAPSE values were 21, 69 and 28, respectively. There was no significant difference in the MR-proANP median value between the group with normal and increased PAP value and RAA (PAP and RAA p value; 0.461, 0.502, respectively). However, there was a significant difference between the groups with reduced and normal TAPSE values (p:0.01). The echo findings of patients with PE and MR-proANP values are displayed in Table 3.

The primary result of the study was that the patients in the case group diagnosed with PE were followed only as discharge and death. Thirty-one patients in the case group died during their treatment. The MR-proANP median (min.-max.) value of the cases that died was 211.05 (114.84-2785.15) pmol/L. In the case group, the number of patients who were discharged after treatment was 69. The median (min.-max.) MR-proANP value of the discharged patients was 275.65 (66.37-3313.08) pmol/L. The comparison of the median MR-proANP values of patients in the case group who died and were discharged showed no significant difference (p:0.207).

Discussion

The current study is the first study evaluating the diagnostic accuracy of the MR-proANP bedside test for acute PE in emergency settings. PE is a life-threatening condition requiring immediate medical attention. Despite technological developments and increased awareness of physicians about PE, there are delays in diagnosis. As a result, PE has high mortality and morbidity caused by PE and reduces healthcare costs.

In acute PE, Right Ventricle (RV) dysfunction may develop as a result of increased pressure in the proximal area of the thrombus. In RV dysfunction, the tension on the cardiac wall increases resulting in natriuretic peptides secretion. In the study conducted by Çelik et al., the N-terminal pro-brain natriuretic peptide (NT-proBNP) level of patients diagnosed with PE was found to be higher than in the control group [11]. In another study on PE, Pro-ANP, BNP, and D-Dimer tests were found to be significantly higher in patients diagnosed with PE complicated with RV dysfunction [12]. In the current study, patients diagnosed with PE were also found to have higher MR-proANP levels. In our study, this result was found to be similar.

Studies on the diagnostic and prognostic value of many biochemical biomarkers in patients with PE have been conducted in recent years. However, there are still a limited number of studies in the literature. In the present study, the MR-proANP value of patients with acute PE in the emergency department was found to be significantly higher (p:0.003). Our results revealed that the median (min.-max.) MR-proANP value in the patient group was 645.8 (66.37-3313.08) pmol/L, while it was 442.9 (226.73-774.78) pmol/L in the control group. In line with the results of our study, it was suggested that MR-proANP is significantly higher in the acute period in PE and can be a parameter that is easy to study.

In the present study, atrial natriuretic peptide (ANP), which is a member of the natriuretic peptide family synthesized primarily in the atrial chambers of the heart, was investigated. Stimulation of ANP release is the result of myocyte stretching rather than transmural pressure load [13]. In a study conducted on patients with dyspnea, the median value of MR-proANP was found to be significantly higher in patients with heart failure among other causes of dyspnea [9]. It has been reported that the increase in MR-proANP levels in PE patients is important in terms of diagnosis, severity and prognosis. In patients with PE, the natriuretic peptide level was found to be significantly higher in patients who died than in those who survived [14]. While the natriuretic peptide level may not be the right method to distinguish PE from acute heart failure, we believe that high MR-proANP levels can be used to diagnose PE. If the patient has a high MR-proANP value, the diagnosis of PE should definitely be considered [10].

Right heart dysfunction can be determined quickly by performing echo to the PE patients. Signs of right heart dysfunction are seen in at least 25% of patients with PE on echo imaging [6]. In a study investigating the mortality of patients diagnosed with PE, it was reported that right heart dysfunction had no influence on mortality [15]. In our study, however, there was no difference in mortality between those with and without right heart dysfunction.

In the study involving PE patients whose CTPA results were investigated, it was reported that factors that adversely affect the prognosis of patients with PE were the RV/LV ratio ≥1 and the TAPSE value <16 mm [16]. A significant value of TAPSE for right heart dysfunction was determined as <16 mm. In a study conducted on the echo findings of PE patients, it was stated that TAPSE was associated with right heart dysfunction [17]. In a study on PE, the RAA was found to be 18±4 cm2 and the PAP value as 46±11 mmHg, and it was considered to be

increased [18]. In line with the current medical literature, our results revealed that an increase in the RAA and a decrease in the value of TAPSE were indicators of right heart dysfunction, but it did not provide any information on 30-day mortality.

Cor pulmonale occurs as a result of pulmonary hypertension that develops due to increased resistance in front of pulmonary flow. Lung diseases may result in cor pulmonale by causing pulmonary hypertension [19]. In the study by Pervez et al., the MR-proANP value in the blood taken on the second day was found to be significantly higher than on the first day in 23 of 83 patients hospitalized for CPD exacerbation [20]. Similarly, the present study revealed that patients with RV dysfunction had high MR-proANP values.

Limitations

The present study had three limitations. First, since MR-proANP is a new biochemical marker and it is not exactly known how it could be affected by comorbidity and medications. Second, the size and location of the thrombus vary from patient to patient, hence the level of right heart dysfunction. Therefore, the amount of MR-proANP release may have differed since the right heart tension level of each patient is different. Third, some of the patients in the case group were undiagnosed during the acute phase of PE due to not presenting to the hospital at the onset of symptoms. Besides, echo could not been performed during the acute phase of the embolism because some patients did not present to the emergency room at the acute phase of their complaints.

Conclusion

We believe that MR-proANP is a fast, simple and non-invasive biochemical test. Also, more studies are needed to make it a diagnostic marker. We believe that future studies will confirm our results.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

References

1. Wood KE. Major pulmonary embolism: review of a pathophysiologic approach to the golden hour of hemodynamically significant pulmonary embolism. Chest. 2002;121(3):877-905. DOI: 10.1378/chest.121.3.877.

2. Kara H. . Acilde akut pulmoner emboli tanı ve tedavisi (Diagnosis and treatment of acute pulmonary embolism in emergency). In: Bayır A, editors. Pulmoner Aciller (Pulmonary Emergencies). 1st ed.Ankara: Türkiye Klinikleri; 2019. p.22- 35.

3. Essien EO, Rali P, Mathai SC. Pulmonary Embolism. Med Clin North Am. 2019;103(3):549-64. DOI: 10.1016/j.mcna.2018.12.013.

4. Miniati M, Prediletto R, Formichi B, Marini C, Di Ricco G, Tonelli L, et al. Accuracy of clinical assessment in the diagnosis of pulmonary embolism. Am J Respir Crit Care Med. 1999;159(3):864-71. DOI: 10.1164/ajrccm.159.3.9806130.

5. Wells PS, Anderson DR, Rodger M, Ginsberg JS, Kearon C, Gent M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. Thromb Haemost. 2000;83(3):416-20.

6. Goldhaber SZ. Echocardiography in the management of pulmonary embolism. Ann Intern Med. 2002;136(9):691-700. DOI: 10.7326/0003-4819-136-9-200205070-00012.

7. de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. Life Sci. 1981;28(1):89-94. DOI: 10.1016/0024-3205(81)90370-2.

8. Rosenzweig A, Seidman CE. Atrial natriuretic factor and related peptide hormones. Annu Rev Biochem. 1991;60:229-55. DOI: 10.1146/annurev.bi.60.070191.001305.

9. Öner Ö, Deveci F, Telo S, Kuluöztürk M, Balin M. MR-proADM and MR-proANP levels in patients with acute pulmonary embolism. J Med Biochem. 2020;39(3):328-35. DOI:10.2478/jomb-2019-0049.

10. Heining L, Giesa C, Ewig S. MR-proANP, MR-proADM, and PCT in Patients Presenting with Acute Dyspnea in a Medical Emergency Unit. Lung. 2016;194(2):185-91. DOI:10.1007/s00408-015-9837-0.

11. Celik Y, Yardan T, Baydin A, Demircan S. The role of NT-proBNP and Apelin in the assessment of right ventricular dysfunction in acute pulmonary embolism. J Pak Med Assoc. 2016;66(3):306-11.

12. Gutte H, Mortensen J, Jensen CV, von der Recke P, Petersen CL, Kristoffersen US et al. ANP, BNP and D-dimer predict right ventricular dysfunction in patients with acute pulmonary embolism. Clin Physiol Funct Imaging. 2010;30(6):466-72. DOI: 10.1111/j.1475-097X.2010.00967.x.

13. Mizuno Y, Yoshimura M, Harada E, Nakayama M, Sakamoto T, Shimasaki Y, et al. Plasma levels of A- and B-type natriuretic peptides in patients with hypertrophic cardiomyopathy or idiopathic dilated cardiomyopathy. Am J Cardiol. 2000;86(9):1036-40. DOI:10.1016/s0002-9149(00)01147-4.

14. Kiely DG, Kennedy NS, Pirzada O, Batchelor SA, Struthers AD, Lipworth BJ. Elevated levels of natriuretic peptides in patients with pulmonary thromboembolism. Respir Med. 2005;99(10):1286-91. DOI:10.1016/j.rmed.2005.02.029.

15. Hakemi EU, Alyousef T, Dang G, Hakmei J, Doukky R. The prognostic value of undetectable highly sensitive cardiac troponin I in patients with acute pulmonary embolism. Chest. 2015;147(3):685-94. DOI:10.1378/chest.14-0700.

16. Kayrak M, Erdoğan HI, Solak Y, Akilli H, Gül EE, Yildirim O, et al. Prognostic value of neutrophil to lymphocyte ratio in patients with acute pulmonary embolism: a retrospective study. Heart Lung Circ. 2014;23(1):56-62. DOI: 10.1016/j.hlc.2013.06.004.

17. Pruszczyk P, Goliszek S, Lichodziejewska B, Kostrubiec M, Ciurzyński M, Kurnicka K, et al. Prognostic value of echocardiography in normotensive patients with acute pulmonary embolism. JACC Cardiovasc Imaging. 2014;7(6):553-60. DOI: 10.1016/j.jcmg.2013.11.004.

18. Khan UA, Aurigemma GP, Tighe DA. Vector velocity imaging echocardiography to study the effects of submassive pulmonary embolism on the right atrium. Echocardiography. 2018;35(2):204-10. DOI: 10.1111/echo.13753.

19. Çiftçi U, Köktürk N, Demir N, Oğuzülgen K, Ekim N. Pulmoner emboli kuşkusu olan hastalarda üç farklı klinik olasılık yönteminin karşılaştırılması (Comparison of three different clinical probability methods in patients with suspected pulmonary embolism). Tüberküloz ve Toraks/ Tuberculosis and Thorax. 2005;53(3): 252-8.

20. Pervez MO, Winther JA, Brynildsen J, Strand H, Christensen G, Høiseth AD, et al. Prognostic and diagnostic significance of mid-regional pro-atrial natriuretic peptide in acute exacerbation of chronic obstructive pulmonary disease and acute heart failure: data from the ACE 2 Study. Biomarkers. 2018;23(7):654-63. DOI: 10.1080/1354750X.2018.1474258.

How to cite this article:

Ertuğrul Altuğ, Hasan Kara, Ayşegül Bayır, Ahmet Ak, Seyit Ali Kayış, Ali Ünlü, Bülent Behlül Altunkeser, Mustafa Koplay, Abdullah Tunçez, Hüseyin Tezcan. *Diagnostic value of mid-regional pro-atrial natriuretic peptide (MR-proANP) level in patients with acute pulmonary embolism. Ann Clin Anal Med 2023;14(1):21-24*

This study was approved by the Ethics Committee of Selcuk University (Date: 2018-03-16, No: 2018/153)